Radiation-induced Alkylation, Hydroxyalkylation, and Reduction of Pyridinecarboxamides in Acidic Alcoholic Solutions

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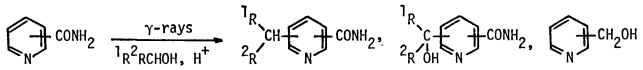
Synopsis. The γ-irradiation of pyridinecarboxamides in acidic methanol or ethanol brings about substitution of the ring hydrogen by alkyl or hydroxyalkyl groups derived from the solvent alcohols in relatively high G-values. In 2-propanol, little alkylation and hydroxyalkylation occur and reduction of $CONH_2$ to CH_2OH occurs in low G-values.

In spite of their biological importance, the radiation-induced reactions of pyridinecarboxamides have not yet been thoroughly studied, at least on the basis of product analyses. Concerning the radiation-induced reactions of model compounds for NAD (nicotinamide dinucleotide), hydroxylation in aqueous solutions[1] and dimer formation[2] have been reported. By means of pulse radiolysis technique, intermediates formed in the radiolysis of pyridinecarboxylic acid derivatives in aqueous alcohol were studied,[3,4] but the reports have not mentioned the structures of products. As an extension of our studies on photo- and radiation-induced reactions of pyridinecarboxylic acid derivatives,[5] we report here the radiation-induced reactions of pyridinecarboxamides, including biologically important 3-pyridinecarboxamide, in acidic alcohols. The radiation-induced reactions may furnish a useful synthetic method, owing to the specific type of reactions, which are different from those induced by a free radical initiator, and their relatively high G-values.

Results and Discussion

Gamma-irradiation of pyridinecarboxamides in acidic alcoholic solutions brings about substitution of the ring hydrogen by alkyl and hydroxyalkyl groups derived from the solvent alcohols and reduction of $CONH_2$ to CH_2OH.



The radiation-induced reactions of pyridinecarboxamides are very similar to those of the corresponding carboxylic esters: 1) In acidic methanolic solutions, 2- and 3-pyridinecarboxamides give methylation products in relatively high G-values. The positions for methylation in carboxamides are similar to those of the corresponding carboxylic esters. 2) In acidic methanol, 4-pyridinecarboxamide undergoes hydroxymethylation rather than methylation. 3) In acidic 2-propanol little isopropylation occurs and, instead, reduction of $CONH_2$ at 2- and 4-positions to CH_2OH occurs.

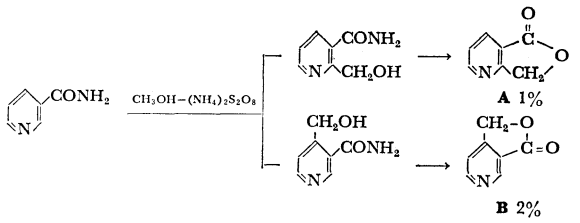
The following differences between the radiation-induced reactions of pyridinecarboxamides and those of carboxylic esters should be noted: 1) Reduction of $CONH_2$ at 2- and 4-positions to CH_2OH is much less efficient than that of the esters. 2) During the irradiation of 3-pyridinecarboxamide in acidic 2-propanol, 6-ethyl-3-pyridinecarboxamide was obtained in higher yield than 6-isopropyl-3-pyridinecarboxamide.

The similarities of the reactions of amides and esters suggest that the mechanism for the radiation-induced reactions of pyridinecarboxamides should be parallel to that of pyridinecarboxylic esters:[5] for alkylation and reduction, hydroxyalkyl radicals and hydrogen atom play important roles. The fact that ethylation occurs more effectively than isopropylation in γ-irradiation of 3-pyridinecarboxamide in 2-propanol suggests that $CH_3\dot{C}HOH$ radical formed by C–C cleavage of 2-propanol is more efficient for alkylation than $(CH_3)_2\dot{C}OH$ radical which is formed predominantly during γ-irradiation of 2-propanol.[6] In the free radical reaction initiated by the thermal decomposition

TABLE 1. RADIATION-INDUCED REACTIONS OF PYRIDINECARBOXAMIDES IN ACIDIC ALCOHOLIC SOLUTIONS
[Pyridinecarboxamide] = 0.03 mol dm^{-3}; [H_2SO_4] = 0.05 mol dm^{-3}; dose rate, 5×10^5 rad h^{-1}; dose, 1.0×10^7 rad.

Substrate	Alcohol	Product (G-value)			
		Substitution product (Position and group introduced)		Reduction product	
2-Pyridinecarboxamide	MeOH	4-Methyl-	(0.55)		
		4-Methyl-6-hydroxymethyl	(0.28)		
	i-PrOH	—		2-Pyridylmethanol	(0.02)
3-Pyridinecarboxamide	MeOH	4-Methyl-	(0.26)		
		6-Methyl-	(0.97)		
	EtOH	6-Ethyl-	(1.04)		
	i-PrOH	6-Isopropyl-	(0.06)		
		6-Ethyl-	(0.14)		
4-Pyridinecarboxamide	MeOH	2-Hydroxymethyl-	(0.22)		
	i-PrOH	—		4-Pyridylmethanol	(0.13)

of ammonium peroxodisulfate,[7] 3-pyridinecarboxamide gives 2- and 4-hydroxymethyl-3-pyridinecarboxylic acid lactones (5,7-dihydrofuro[3,4-*b*]pyridin-5-one (**A**) and 1,3-dihydrofuro[3,4-*c*]pyridin-3-one (**B**)), which are the intramolecular alcoholysis products from 2- and 4-hydroxymethyl-3-pyridinecarboxamides in low yields.



The γ-irradiation of pyridinecarboxamides and esters in methanol (and in the case of 3-pyridinecarboxamide in ethanol) gives methylation (and ethylation) products in rather high *G*-values and methylation by methanol can not be effected by an efficient free radical initiator $S_2O_8^{2-}$. Therefore, this type of radiation-induced alkylation should have synthetic utility for the introduction of alkyl groups to the pyridine nucleus.

Experimental

Materials. Commercial 2-, 3-, and 4-pyridinecarboxamides were used after the purification by recrystallization.

Gamma-irradiation. Solutions containing 0.03 mol dm^{-3} of pyridinecarboxamide and 0.05 mol dm^{-3} of H_2SO_4 were deaerated by bubbling Ar for 30 min. The solutions were irradiated at the ^{60}Co γ-facility of Japan Atomic Energy Research Institute in Takasaki (dose rate, 5×10^5 rad h^{-1}; dose, 1.0×10^7 rad).

$(NH_4)_2S_2O_8$-induced Reaction. A methanolic solution (50 cm^3) containing 3-pyridinecarboxamide (15 mmol), $(NH_4)_2S_2O_8$ (15 mmol), and H_2SO_4 (0.4 cm^3) was refluxed for 30 min.

Separation of Products. The irradiated solutions were concentrated under reduced pressure and neutralized with Na_2CO_3 and $NaHCO_3$. The products were separated by means of TLC (plate, Kieselgel 60 GF_{254} of E. Merck Co.; developing solvents; ethyl acetate, acetone, and their mixture).

Identification of Products. 4-Methyl-2-pyridinecarboxamide: mp 119—120 °C; IR (KBr disk) 3400, 3250, 1680 and 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.40 (1H, d, J=4.4 Hz, H at 6-position), 8.02 (1H, d, J=1 Hz, H at 3-position), 7.23 (1H, dd, J=4.4 and 1 Hz, H at 5-position), and 2.44 (3H, s, CH_3); Found: C, 61.4; H, 6.2; N, 20.3%; Calcd for $C_7H_8N_2O$: C, 61.8; H, 5.9; N, 20.6%.

6-Ethyl-3-pyridinecarboxamide: mp 161—163 °C; IR (KBr disk) 3220, 1690, 1405, 1395, and 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.84 (1H, d, J=2.0 Hz, H at 2-position), 8.09 (1H, dd, J=8.0 and 2.0 Hz, H at 4-position), 7.40 (1H, d, J=8.0 Hz, H at 5-position), 2.88 (2H, q, J=7.2 Hz, CH_2), and 1.30 (3H, t, J=7.2 Hz, CH_3); Found: C, 63.7; H, 6.7; N, 18.9%. Calcd for $C_8H_{10}N_2O$: C, 64.0; H, 6.7; N, 18.7%.

2-Hydroxymethyl-4-pyridinecarboxamide: mp 183—184.5 °C; IR (KBr disk) 3360, 3320, 1690, 1420, and 1040 cm^{-1}; ^1H NMR δ=8.56 (1H, d, J=5 Hz, H at 6-position), 7.74 (1H, d, J=1 Hz, H at 3-position), 7.56 (1H, dd, J=5 and 1 Hz, H at 5-position), and 4.80 (2H, s, CH_2); Found: C, 55.0; H, 5.6; N, 19.0%. Calcd for $C_7H_8N_2O_2$: C, 55.3; H, 5.3; N, 18.4%.

6-Isopropyl-3-pyridinecarboxamide (mp 135—136.5 °C) was identified only on the basis of ^1H NMR because of its low yield. ^1H NMR (D_2O) δ=8.80 (s), 8.05 (d, J=8 Hz), 7.35 (d, J=8 Hz), 3.00 (m, J=8 Hz), and 1.23 (d, J=8 Hz).

2-Hydroxymethyl-3-pyridinecarboxylic acid lactone: mp 108—111 °C; IR (KBr disk) 1760 cm^{-1} (γ-lactone C=O); ^1H NMR ($CDCl_3$) δ=8.85 (1H, dd, J=5.2 and 2.0 Hz, H at 6-position), 8.28 (1H, dd, J=7.6 and 2.0 Hz, H at 4-position), 7.45 (1H, dd, J=7.6 and 5.2 Hz, H at 5-position), and 5.33 (2H, s, CH_2); MS (70 eV) *m/e* (relative intensity) 135 (M^+; 58), 106 (100), 78 (38), 77 (22), and 51 (11); Found: *m/e* 135.0323. Calcd for $C_7H_5NO_2$: M, 135.0320.

4-Hydroxymethyl-3-pyridinecarboxylic acid lactone: mp 122—124 °C; IR (KBr disk) 1760 cm^{-1} (γ-lactone C=O); ^1H NMR ($CDCl_3$) δ=9.19 (1H, s, H at 2-position), 8.87 (1H, d, J=5 Hz, H at 6-position), 7.52 (1H, d, J=5 Hz, H at 5-position), and 5.38 (2H, s, CH_2); MS (70 eV) *m/e* (relative intensity) 135 (M^+; 100), 106 (66), 78 (37), and 51 (12); Found: *m/e* 135.0320. Calcd for $C_7H_5NO_2$: M, 135.0320.

4-Methyl-3-pyridinecarboxamide (mp 163.5—164.5 °C; lit, [8] 167—167.5 °C) and 6-methyl-3-pyridinecarboxamide (mp, 199—200 °C; lit,[9] 196—198 °C) were identified by means of melting point measurements and NMR and IR spectral analyses. Pyridylmethanols were identified by the accordance of the gas-chromatographic and spectral properties with the authentic ones.

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